Pediatric Clinics of North America
Volume 49 • Number 5 • October 2002

Bone marrow failure syndromes in children

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PII S0031-3955(02)00031-7

Introduction

The term "**bone** marrow failure" or "aplastic anemia" encompasses peripheral blood single cytopenias as well as pancytopenia, due to inability of the **bone** marrow to effectively produce blood cells. While acquired aplastic anemias are more common, it is possible that they occur in rare individuals who are genetically predisposed to marrow damage. At least 25% of childhood aplastic anemia is on a background of known marrow failure genes; these patients must be identified, since the inherited and acquired disorders differ significantly in treatment and prognoses.

This chapter will review homozygotes for autosomal recessive **bone** marrow failure genes, heterozygotes for autosomal dominant genes, and hemizygotes for X-linked genes (Table 1) . Each of the disorders has a "typical" phenotype; the challenge is to identify patients when they are not typical. Most of these diagnoses will only be thought of by physicians who have previously seen or at least read about them. As Louis Pasteur said, "Chance comes to the prepared mind". More complete information about these disorders can be found elsewhere [1] [2] .

Table 1. Inherited bone marrow failure syndromes

Syndrome	N	Genetics
Fanconi's anemia	1200	Autosomal recessive
Diamond-Blackfan anemia	1000	Autosomal dominant, recessive, sporadic
Dyskeratosis congenita	300	X-linked recessive, autosomal recessive, Dominant
Shwachman-Diamond syndrome	350	Autosomal recessive

Thrombocytopenia absent radii	200	Autosomal recessive
Severe congenital neutropenia	300	Autosomal recessive
Amegakaryocytic thrombocytopenia	75	Autosomal recessive
Pearson's syndrome	50	Mitochondrial

N, approximate number of cases reported in the literature.

Pancytopenias

This group of disorders includes those in which it is common for all three lineages to fail, although patients may present initially with deficiency in only a single lineage. Many of the patients with these disorders may have non-hematologic signs or symptoms which could (and should) lead to the appropriate diagnosis in the absence of hematologic problems, but which are also consistent with other diagnoses, until the hematologic manifestations appear.

Fanconi's anemia

Fanconi described three brothers with aplastic anemia and physical abnormalities in 1927, which led later clinicians who saw similar cases to name the syndrome after him. Patients have been diagnosed from birth to the fifth decade, with a median age of 8 years, and all racial and ethnic groups are included. The male:female ratio in literature cases is 1.2:1. Birth defects were reported in approximately 75%, and include in decreasing order of frequency: skin hyperpigmentation and café au lait spots, short stature, hypoplastic or absent thumbs or radii, undescended testes and hypogonadism in males, microcephaly, microphthalmia and strabismus, structural renal anomalies, low birth weight, developmental disabilities, hearing loss, and other abnormalities.

The inheritance of Fanconi's anemia (FA) is autosomal recessive, and the carrier frequency ranges from 1/90 in populations with founder effects such as Ashkenazi Jews or Afrikaners, to an estimate of 1/300 in the United States and Europe [3] [4] [5] . The diagnosis of FA homozygotes is confirmed by the detection of chromosome aberrations (breaks, gaps, rearrangements, endoreduplications) in cells (usually blood lymphocytes stimulated with phytohemagglutin) following culture with DNA crosslinking agents such as diepoxybutane (DEB) or mitomycin C (MMC) [6] . In approximately 10% to 15% of patients there is somatic mosaicism, in which some or all of the hematopoietic cells have undergone molecular gene correction [7] [8] .

FA patients are now classified according to their complementation group, which was originally assigned by co-culture of cells from different patients and identification of cell lines which corrected the chromosome breakage of other lines. There are at least 8 groups (Table 2) , *FANCA* through *FANCG*, and the genes have been localized for 7 and cloned for 6 of the groups. Most patients belong to Group A, and most of the mutations in A are unique, except for the Afrikaner founder mutation. Approximately 10% of patients belong to Group C, and there are about a dozen C mutations, including the Ashkenazi Jewish founder mutation. Group assignment can be made by identification of the retroviral vector containing a normal FA gene that corrects the defect in the patient's cells. The specific mutation is then defined by molecular tools such as sequencing. Currently there are only limited data with regard to genotype/phenotype correlations, suggesting that mutations in which there is no gene product are more severe than those with a partial product [9] .

Table 2. Bone marrow failure genes

Disease	Gene	Locus	~% of Patients
Fanconi's anemia	*FANCA*	16q24.3	70
	*FANCB**	N/A	Rare
	FANCC	9q22.3	10
	*FANCD1**	N/A	Rare
	FANCD2	3p25.3	Rare
	FANCE	6p21.3	10
	FANCF	11p15	Rare
	FANCG	9p13	10
Diamond-Blackfan anemia	*RPS19*	19q13.3	25
	N/A	8p23.2-p22	35
	N/A	N/A	40
Dyskeratosis congenita	*DKC1*	Xq28	X-linked males
	DKC2	3q21-28	Dominant
Shwachman-Diamond syndrome	N/A	7q1.1	100
Severe congenital neutropenia	*ELA2*	19p13.3	90
Amegakaryocytic thrombocytopenia	*c-Mpl*	1p35	100
Thrombocytoopenia absent radii	N/A	N/A	N/A
Pearson's syndrome	Mitochondrial DNA, deletions of 2 to 8 kb	100	

* Not yet cloned. N/A, no data available

Evidence suggests that the products of the A, C, E, F, and G genes form a nuclear complex, which then participates in the ubiquitination of the D2 protein, which in turn colocalizes with DNA damage response proteins including BRCA1 [10] [11] . This model helps to explain the similar phenotypes of patients from different genetic groups. FA is one of several diseases in the category of caretaker gene diseases, which includes ataxia telangiectasia (mutant in *ATM,* a DNA damage response protein), Bloom's Syndrome (*BS*, a DNA helicase), xeroderma pigmentosum (7 *XP* genes involved in nuclear excision repair), hereditary nonpolyposis colorectal cancer (5 mismatch repair genes), and hereditary breast/ovarian cancer (*BRCA1* and *BRCA2*, DNA damage response genes).

The earliest and most frequent life-threatening complication in FA (reported in approximately 90%) is aplastic anemia, with usual onset in childhood, manifest by thrombocytopenia, neutropenia, and macrocytic anemia, and associated with a hypocellular fatty bone marrow with decreased myeloid and erythroid precursors and megakaryocytes. The pre-anemic phase may be identified because of macrocytic red cells and increased fetal hemoglobin. *In vitro* hematopoietic cultures from FA marrow cells have decreased colony numbers, suggesting a defect in FA stem cells.

Management of the aplastic anemia is clinically indicated when the Hb drops below 8 g/dl or there is symptomatic anemia, platelets are <30,000/µl, and/or neutrophils are <500/µl. Patients with an HLA-matched sibling donor who does not have FA should be offered **bone** marrow transplant (BMT). Preparation for BMT has been most successful with low dose cyclophosphamide and modified irradiation [12] , and the survival is >70%; with an alternative donor the survival is <40%. Hematopoietic stem cells can be obtained from **bone** marrow, cord blood, or peripheral blood.

Patients without a matched sibling donor should be offered treatment with androgens, usually oxymetholone at 2 to 5 mg/kg/d. More than 50% respond with improved blood counts, and the dose can be titrated to maintain adequate numbers. Side effects of androgens include virilization, liver dysfunction, and liver tumors (□3% of reported FA patients) and treatment should be monitored with physical examinations, liver function tests, and abdominal ultrasound examinations. Liver tumors include adenomas and hepatomas, and are usually not the primary cause of death. Patients who fail to respond to androgens, or who have unacceptable side effects may be offered stem cell transplant from an unrelated donor, but the survival rate is poor [13] . Many patients are also given prednisone at 5 to10 mg on alternate days, but there is no evidence that this achieves the putative benefits of decreasing the early growth acceleration of androgens or reducing the hemorrhagic effects of low platelet counts.

Supportive care for FA patients with cytopenias includes transfusions of packed red cells and platelets, G-CSF for neutropenia, erythropoietin (Ep) usually only for those in whom the renal Ep response to anemia is inadequate, and ε-aminocaproic acid to decrease clot lysis in thrombocytopenic patients. Antibiotic and antifungal treatment should be used when clinically indicated and not prophylactically. Medications such as aspirin that interfere with platelet function should be avoided. Blood product donors should not be relatives, in order to avoid sensitization to minor tissue antigens which might increase the risk of rejection during a subsequent transplant.

The prognosis for FA patients is poor, particularly if they have severe aplastic anemia, and the projected median survival is age 20 years for all patients in the literature, although it has improved to be >30 years of age in cases reported in the last decade.

FA patients are at approximately 6% risk of development of myelodysplastic syndrome (MDS), characterized by cytopenias, dysmyelopoiesis, dyserythropoiesis, and abnormal megakaryocytes. Although many of the patients with MDS have clonal cytogenetic abnormalities, clones have also been seen in FA patients whose **bone** marrows did not appear dyshematopoietic, and there is no evidence so far that MDS will inevitably develop into leukemia [14] . A poor outcome in MDS is associated with the severity of the cytopenias, and not the presence of a clone, and referral for transplant should be made on clinical grounds. The projected median survival age based on the literature is 22 years of age for those with MDS.

Leukemia, usually acute myeloid (AML), was reported in close to 10% of FA patients, only 10% of whom had a previous diagnosis of MDS, and approximately 25% did not have a history of aplastic anemia. AML is difficult to treat in any children, and particularly so in FA. Stem cell transplant offers a possibility of cure, but there is a high risk of recurrence of the leukemia. Treatment of the AML with standard aggressive chemotherapy with DNA-damaging drugs often results in severe toxicity, since all cells in FA patients have a defect in DNA repair. Projected median survival from the literature cases with leukemia is 16 years of age, and death is usually within a year of diagnosis of the leukemia.

For those patients who have escaped the consequences of aplastic anemia, MDS, or leukemia, solid tumors provide a risk that in fact may be inevitable [1] [15] . Approximately 5% of reported FA patients developed cancers involving the head and neck, esophagus, vulva, cervix, skin (non-melanoma), brain, and other less frequent sites. The median age for cancer in FA was 26 years, much younger than those

cancers occur in the general population. As in leukemia, approximately 25% were not diagnosed as FA until they developed a solid tumor. The projected median survival was age 31 for those with cancer. As for leukemia, chemotherapy for solid tumors has substantial toxicity, also radiation treatment, and thus surgery is recommended whenever possible.

Patients whose aplastic anemia or leukemia was cured by **bone** marrow transplant may have increased their risk of cancer. At least 8 cases of tongue cancer were reported at 3 to 15 years following BMT, and the actuarial prediction from one series was 24% by 8 years after BMT [16] . Further studies are necessary to determine whether the risk of cancer after BMT is greater than the risk associated with the natural history of cancer in FA as the patients age.

Minimal recommendations for management of patients with FA are to monitor for cytopenias with blood counts at least as often as every 3 months, and to obtain annual **bone** marrow aspirates, biopsies, and cytogenetics to monitor for development of MDS or leukemia. Birth defects should be dealt with through surgical or medical approaches, with blood product support as needed. Patients on androgens require liver function tests every 2 to 3 months and annual ultrasounds. Head and neck cancer screening should begin by age 10 in untransplanted patients, or within a year after a transplant, and includes annual oral and pharyngeal exams. Esophageal endoscopy should be considered in young adults. Gynecologic exams and cancer screening should begin at menarche or age 16. The usual environmental cancer prevention strategies should be employed, such as avoidance of tobacco, alcohol, and sun exposure.

Prenatal diagnosis can be offered, using cellular-based chromosome breakage tests or DNA-based mutation analyses. Preimplantation genetic diagnosis was successful in resulting in the birth of a non-FA infant who was an HLA-identical match for his sibling [17] .

Dyskeratosis congenita

The diagnostic triad for dyskeratosis congenita (DC) includes reticulated hyperpigmentation of the face, neck and shoulders, and dystrophic nails, which begin in the first decade, and mucous membrane leukoplakia with usual onset in the second decade. Aplastic anemia occurs in half the patients with DC, usually in the second decade, and cancer develops in 10% in the third and fourth decades. The features of DC become more apparent as patients get older.

Here are three distinct patterns of inheritance of DC: presumably X-linked recessive males (XLR); autosomal recessive (AR), and autosomal dominant (AD), with literature cases comprising more than 200, approximately 50, and 7 families respectively. Diagnosis is usually made in teen or early adult years, as the abnormalities of the skin and nails become more apparent, and leukoplakia develops. Other physical manifestations include excessive tearing and loss of eyelashes, dental caries, osteoporosis, intracranial calcifications, hyperhidrosis, premature grey hair and early hair loss, gastrointestinal strictures and ulcers, and pulmonary fibrosis. Aplastic anemia was reported at a median age of 11 years, in >30% of the XLR cases, more than half of the AR cases, and rarely in the AD form, which is generally milder. In one series of XLR patients, however, the actuarial probability of aplastic anemia was 94% by 40 years of age [18] . All of these data may be overestimates, since DC patients without hematologic complications may not be referred to hematologists or reported in the literature.

The laboratory features of the aplastic anemia in DC are similar to the findings described above for FA. The diagnostic test for FA, chromosome breakage in the presence of DEB or MMC, is normal in DC, although there is some evidence that there is chromosomal instability in cultured fibroblasts [19] .

Hematopoietic stem and progenitor numbers are low or absent, and responses to growth factors *in vitro* are not consistently effective.

The X-linked form of DC maps to Xq28 (Table 2) , and multiple mutations have been identified in the gene *DKC1*, which codes for a nucleolar protein dyskerin [20] . The role of dyskerin is not clear, but it may be involved in ribosomal assembly and RNA production. It binds to telomerase, and may be important for maintenance of telomere length, which is shortened in DC [21] [22] . The gene for dominant DC, *DKC2*, was found to be the RNA component of telomerase, hTR [23] . The authors suggest that **bone** marrow failure in DC is due to haploinsufficiency for telomerase, and that normal cells have a selective growth advantage.

The mortality rate is high in DC, due to aplastic anemia or cancer. The aplastic anemia may require treatment by **bone** marrow transplant, but the overall survival is less than 30%, whether the donor is matched-related or mismatched or unrelated. Some of the deaths were due to late developments of mucositis or venoocclusive disease, and it is speculated that there may be toxicity from preparation with cyclophosphamide or radiation [24] . Medical management of the **bone** marrow failure includes androgens as in FA, with perhaps a benefit from the addition of erythropoietin and G-CSF [25] .

Cancer was reported in close to 15% of the literature cases. The majority were squamous cell carcinomas of the oropharyngeal and gastrointestinal regions, at a median age of 30 years, similar to FA. Leukemia and MDS also occur in DC, but are less common.

Syndromes that have some features of DC include Hoyeraal-Hreidarsson Syndrome (HHS) (males with aplastic anemia, growth retardation, cerebellar hypoplasia and immunodeficiencies) and Revesz Syndrome (RS) (dystrophic nails, leukoplakia, aplastic anemia, growth retardation, cerebellar hypoplasia, and microcephaly, and bilateral exudative retinopathy. The genetic defect in HHS is mutant *DKC1*, while the defect in RS has not been identified.

Shwachman-Diamond syndrome

The combination of congenital pancreatic insufficiency and neutropenia leads to the diagnosis of Shwachman-Diamond (SD) Syndrome, which has been reported in more than 300 cases [26] . Although the problems of malabsorption are present very early, more than 40% develop marrow failure. Useful tests to confirm the diagnosis include low serum trypsinogen, fatty pancreas on imaging studies, and metaphyseal dysostosis. The inheritance is autosomal recessive [27] , and the gene has been mapped to the centromere of chromosome 7 (Table 2) [28] .

Neutropenia is below 1500/μl on more than three occasions, although it may be chronic, intermittent, or cyclic. There may be an evolution to thrombocytopenia, anemia, or full-blown aplastic anemia. **Bone** marrow has a myeloid arrest and may be hypocellular, and hematopoietic colony formation is poor. There may be increased marrow apoptosis [29] . Chromosome breakage is normal.

The malabsorption in SD responds to oral pancreatic enzymes. Neutropenia may improve with G-CSF. Patients with trilineage pancytopenia due to aplastic anemia may require **bone** marrow transplant, with a survival of approximately 50% unrelated to the source of the donor stem cells.

The reported frequency of leukemia is approximately 5% to 10%, and all but one of the cases were male, a currently unexplained finding. Most of the leukemias were AML, as in FA, and the median survival age was 14 years for these patients, compared to 35 years for the entire group of SD patients. In one

series of 21 patients, 7 developed MDS, 5 of whom went on to leukemic transformation [30] . In the literature reports, 10% had MDS. Cytogenetic clonal abnormalities were common, and the majority involved chromosome 7, usually as isochromosome 7q [31] . There are no reports of solid tumors in SD so far.

A few other syndromes have some features that overlap with those of SD. Cartilage-hair-hypoplasia (CHH) is an autosomal recessive chrondrodysplasia with metaphyseal dysostosis, and short limbed dwarfism, in which there may be neutropenia, macrocytic anemia, and lymphopenia. There is a 7-fold increase in malignancies [32] . Mutations were found in the RNA component of Rnase MRP, which is located at 9p21-p13 [33] . Pearson's Syndrome consists of exocrine pancreatic dysfunction, acidosis, neutropenia, refractory sideroblastic anemia, and vacuolization of marrow precursors [34] . The molecular defect is a set of deletions of various sizes of mitochondrial DNA, which includes the respiratory enzyme genes [35] . Reticular dysgenesis is a rare autosomal recessive disorder with congenital absence of neutrophils and monocytes, lymphopenia, and absent cellular and humoral immunity [36] . **Bone** marrow transplant may be effective.

Amegakaryocytic thrombocytopenia (Amega)

These patients present in infancy with thrombocytopenia, without birth defects characteristic of FA or other syndromes. They may have macrocytic anemia, and close to half of the reported cases progressed to aplastic anemia. **Bone** marrow has normal cellularity with decreased or absent megakaryocytes, and megakaryocyte progenitors are decreased, while serum levels of thrombopoietin are elevated [37] . Chromosome breakage testing is normal.

The defect is related to mutations in the gene for the thrombopoietin receptor, *c-mpl*, which maps to 1p35 [38] . The inheritance is autosomal recessive, and both *c-mpl* genes have mutations in affected individuals.

Aplastic anemia develops by a median age of 3 years, and the hematologic problems can be cured by stem cell transplant. Leukemia has been noted occasionally.

Prenatal diagnosis has been done by detection of thrombocytopenia in fetal blood obtained by cordocentesis, and can now be done using DNA-based mutation analyses.

Familial marrow dysfunction

There is a large number of patients whose **bone** marrow failure appears to be congenital and familial, although in many cases no specific label can be applied. Details can be found in more comprehensive reviews, but the disorders will be mentioned here in the hope of stimulating consideration of these entities where appropriate [1] [2] .

Autosomal dominant conditions with physical anomalies include the IVIC Syndrome, with radial ray hypoplasia, strabismus, deafness, and thrombocytopenia, also known as oculootoradial syndrome [39] [40] . Another is the WT Syndrome, with radial-ulnar hypoplasia, abnormal thumbs and fingers, and cytopenias or leukemia [41] [42] . Four families were reported with radio-ulnar synostosis and aplastic anemia, thrombocytopenia, or leukemia; the most recent cases had a mutation in a gene involved in **bone** morphogenesis, *HOXA11* [43] [44] . Families with the ataxia-pancytopenia syndrome have cerebellar atrophy, aplastic anemia, and leukemia [45] [46] .

There are a few reports of autosomal dominant, autosomal recessive, and X-linked recessive families with aplastic anemia and/or leukemia without physical abnormalities, as well as several families with apparent autosomal recessive inheritance with physical findings that were not characteristic of known syndromes [1] [47] [48] [49] .

Other known syndromes

A few cases of aplastic anemia have been reported in other syndromes, in which hematologic complications are not a common component of the phenotype. They are included here in order to remind us that having one syndrome does not preclude either a different syndrome, or a rare but real complication of the initial syndrome whose frequency is unknown. Space does not permit more than a mention of these with referral elsewhere for more details [1] [2] . Five patients with known Down Syndrome developed aplastic anemia. Six patients with Dubowitz Syndrome had aplastic anemia, and 3 had lymphoid malignancies. Twenty-five percent of reported cases of Seckel Syndrome had aplastic anemia or malignancies. Amegakaryocytic thrombocytopenia as well as leukemia was reported in several cases of Noonan's Syndrome.

Single cytopenias

Diamond-Blackfan anemia

Congenital pure red cell aplasia was first described in the late 1930s by Josephs, and Diamond and Blackfan [50] [51] , and is currently known as Diamond-Blacklfan Anemia (DBA). It is a normochromic, usually macrocytic anemia with reticulocytopenia, normocellular **bone** marrow with erythroid hypoplasia, normal or slightly decreased leukocytes, and normal or increased platelets. There are more than 1000 cases reported in the literature in varying degrees of detail. The diagnosis is usually made in infancy, with 10% diagnosed at birth, 50% by 3 months, and 90% by 18 months; the oldest was diagnosed at age 64 years.

Clinical histories are compatible with approximately 25% autosomal dominant or autosomal recessive, and the majority sporadic cases. Recent molecular analyses combined with detection of macrocytosis and increased red cell adenosine deaminase (ADA) suggest that many of the apparently sporadic cases may be dominant with variable penetrance [52] .

More than one-fourth of DBA patients have physical abnormalities, including typical facies, cleft lip or palate, micrognathia, flat thenar eminences and weak radial pulses, triphalangeal or otherwise abnormal thumbs, short stature, hypertelorism and other eye anomalies, renal abnormalities, and other findings. The anemia may be as low as a Hb of 1.5 g/dl. As in the other marrow failure syndromes, red cells are usually macrocytic for age, with increased fetal hemoglobin and fetal "i" antigen. **Bone** marrows are cellular, with reduced or absent red cell precursors. Serum levels of hematinics such as erythropoietin, iron, ferritin, folic acid, and B12 are all elevated. The majority of the patients have high levels of red cell ADA [53] , which helps to distinguish DBA from TEC (see later), but is only confirmatory, since a few otherwise typical DBA patients have normal ADA. Peripheral blood chromosomes are normal, without increased breaks.

The numbers of erythroid progenitors are reduced, although colony formation can be increased with high levels of erythropoietin or other hematopoietic factors such as stem cell factor [54] . DBA marrow cells undergo accelerated apoptosis, which could be prevented by erythropoietin [55] . No mutations were

found in the *c-kit, SCF,* or erythropoietin receptor genes.

Patients with X;19 translocation or microdeletion syndromes involving 19q13.2 led to identification of one DBA gene as *RPS19* (Table 2) , which codes for ribosomal protein subunit 19. Haploinsufficiency of *RPS19* explains many of the dominant cases in which there is variable penetrance [52] . This gene was found to be mutant in approximately 25% of patients. The role of RPS19 in erythropoiesis is not yet defined. A second DBA gene has been mapped to 8p23.2-p22 in approximately 35% of patients [56] , and thus there must be at least one more DBA gene.

The current therapeutic approach is to treat DBA patients with corticosteroids, usually prednisone at 2 mg/kg/day until there is a rise in Hb to above 8 g/dl, followed by a gradual reduction in dose and shift to alternate days, in order to reduce the growth retardation and other side effects of steroids. Although more than 50% of DBA patients will respond to steroids, some will relapse or suffer serious side effects, including diabetes and aseptic necroses of femoral or humeral heads. For some adolescents, a "steroid holiday" is desirable, to permit a growth spurt and have a more normal appearance during those sensitive years. These patients and the steroid non-responders or steroid failures require transfusions, with leukocyte-depleted packed red cells every 3 to 6 weeks, to maintain nadir hemoglobins above 6 g/dl. Iron overload requires daily chelation with subcutaneous desferrioxamine using the same protocols as are used for thalassemia [57] .

Hematopoietic stem cell transplant offers an alternative to transfusion for those for whom steroids are inadequate. The survival in the cases in the literature was 75% among those with matched sibling donors, and 40% for a smaller number with alternative donors [58] ; it was 88% and 14% respectively in cases in the Diamond-Blackfan Anemia Registry [59] .

The median actuarial survival in the literature cases was age 43, but reached age 65 in those reported in the last decade. Thus the long term prognosis for DBA is significantly better than for the **bone** marrow failure syndromes discussed so far. However, DBA patients are also at risk of malignant diseases. Ten cases of leukemia were reported, all but one AML. Three patients had MDS, one of whom evolved to leukemia. Close to 20 patients developed non-hematologic cancers, including 5 osteogenic and one soft tissue sarcoma, two Hodgkin's and one non-Hodgkin's lymphoma, two breast cancers, and one each of several other solid tumors.

Prenatal diagnosis of DBA is possible by detection of anemia in utero using Doppler blood flow, or by obtaining fetal blood by cordocentesis and demonstration of low Hb, increased MCV, elevated red cell ADA, reduced erythroid progenitors, or mutations in RPS19.

Transient erythroblastopenia of childhood

Although this disorder is acquired and not inherited, it is included in order to distinguish patients with DBA from those with transient erythroblastopenia of childhood (TEC). There are more than 500 cases in the literature, with temporary anemia, reticulocytopenia, and marrow erythroblastopenia. The median age is 2 years, and more than 80% of the cases are older than one year at diagnosis. There is often an antecedent viral illness. TEC patients do not have birth defects. There may be an associated transient neutropenia in 20% of cases. Red cell ADA is normal. The MCV, Hb F, and i antigen are normal at diagnosis, rise during recovery, and then normalize as the Hb level is restored. No virus has been proven to be causal, despite several studies that ruled out the candidate parvovirus. Marrow erythroid progenitors are often decreased, and many patients have serum or cellular inhibitors of erythropoiesis.

TEC is indeed transient, with most patients demonstrating spontaneous improvement within one to two months. Transfusions were required in approximately half the patients, but usually only a single transfusion was sufficient. There is no role for immunosuppressive treatment.

Severe congenital neutropenia

Severe congenital neutropenia (SCN) is diagnosed in infants with a history of pyogenic infections and neutrophil counts below 200/µl. There are approximately 300 cases reported. The first description by Kostmann in 1956 included several cases in a very large intermarried kinship in Northern Sweden [60], which led to the impression that this disease has an autosomal recessive inheritance pattern. However, the recent cloning of the neutrophil elastase 2 gene (ELA2) and the identification of heterozygous mutations in patients with SCN indicates that the inheritance may be autosomal dominant [61].

The neutropenia is marked, although eosinophils and monocytes may be elevated. **Bone** marrows have normal cellularity, with absent or decreased myeloid precursors, and a maturation arrest at the myelocyte or promyelocyte stage. Myeloid progenitors are also decreased, and form colonies with early myeloid precursors, eosinophils, and monocytes. *In vitro* myelopoiesis was improved by the addition of stem cell factor.

Prior to the use of G-CSF, the expected median survival was 3 years, due to early deaths from infection. Subcutaneous G-CSF has been available since 1989 [62]. The dosage of 5 to 10 µg/kg/day has led to improved neutrophil counts in more than 90% of patients, and changed the natural history of the disease. One possible side effect has been osteoporosis, which may actually be an intrinsic part of the syndrome [63]. A more serious potential complication is the development of leukemia (13%) or MDS (7%) [64]. There were only 4 cases of leukemia in patients who did not receive G-CSF. In patients who were treated with G-CSF, the most frequent clonal cytogenetic finding was monosomy 7. Many of these patients also are heterozygous for activating *ras* mutations, as well as point mutations in the receptor for G-CSF [65] [66], which may precede the devlopment of leukemia.

Prenatal diagnosis based on neutropenia is difficult, since fetal neutrophil counts are already low, but DNA-based analyses of mutations in ELA2 may now be identified.

Thrombocytopenia with absent radii

More than 200 cases of thrombocytopenia with absent radii (TAR) have been reported. Patients are usually diagnosed at birth, due to thrombocytopenia associated with radial aplasia with thumbs present (whereas in FA thumbs are missing if there is radial aplasia). Other physical findings may include abnormal fingers, absent or short ulnae, abnormal humeri, lower limb anomalies, congenital heart disease, and gonadal anomalies. Twenty percent had bloody diarrhea, which might have been due to allergy to cow's milk.

Platelet counts are <50,000/µl at diagnosis, anemia is due to bleeding, and more than one-third may have leukocyte counts >40,000/µl, due to a transient benign leukemoid reaction. There may be splenomegaly from extramedullary hematopoiesis. **Bone** marrow cellularity is normal, with normal or increased myeloid and erythroid precursors, and absent or abnormal megakaryocytes. Chromosome breakage is not increased. Hematopoietic cultures are normal for myeloid and erythroid colonies, with usually absent megakaryocyte progenitors. Serum levels of thrombopoietin are elevated, as in amegakaryocytic thrombocytopenia.

Inheritance appears to be autosomal recessive, although there are fewer consanguineous families than expected. No mutations have been found in the *c-mpl* gene.

The prognosis in TAR is better than in any of the other inherited **bone** marrow failure syndromes. The hematopoietic defect is restricted to the platelet lineage. Most patients have an improvement in the platelet count after the first year, although they may require platelet transfusions to maintain a count above 10 to 15,000/μl during that interval. Actuarial survival reaches a plateau of 75% by age 4 years. As in FA patients, ε-aminocaproic acid may be helpful during bleeding episodes. **Bone** marrow transplant is rarely needed, but was successful in one patient with an intracranial hemorrhage [67]. Cancer may be coincidental, since only 3 patients have been reported, a child with acute lymphoblastic leukemia, an infant with stage D(S) neuroblastoma, and an adult with ileal, ovarian, and bladder carcinomas beginning at age 67.

Prenatal diagnosis of TAR can be made by the concomitant observation on ultrasound of radial aplasia with thumbs present, and thrombocytopenia in fetal blood.

Summary

There are several common themes that are emerging from our expanding knowledge about the inherited **bone** marrow failure syndromes. Patients have a spectrum of birth defects, which are relatively characteristic for each syndrome, but overlap in features such as poor growth, radial ray anomalies, and involvement of skin, eyes, renal, cardiac, skeletal, and other organs. Within each syndrome the composition and severity of the physical phenotype varies widely, and it may require the astute observer to make the correct diagnoses in the milder cases. There is also a wide spectrum to the hematologic picture. These range from single cytopenias such as DBA, SCN, and TAR, which do not develop pancytopenia, to SD and Amega patients who begin with deficiency of a specific single lineage, but evolve to aplastic anemia, to patients with FA or DC, who may present with a deficiency of any one of the cell lines, but almost inevitably end up with full-blown aplastic anemia. Acute myeloid leukemia has been observed in FA, DBA, DC, SD, SCN, and Amega, although not yet in TAR patients. MDS has also been reported in all of the same disorders as AML, although whether it is a preleukemic condition or an independent **bone** marrow dyspoiesis is not yet clear. Solid tumors are also now appearing in patients whose underlying disease involves hematopoiesis and physical development. These tumors occur at much younger ages than in the general population, in patients who do not appear to have the usual risk factors, and have patterns that are characteristic to the syndrome, such as head and neck and gynecologic cancers in FA and DC, and osteogenic sarcomas in DBA. The other syndromes have not yet been reported to have a propensity for solid tumors.

Several genes have been identified that are mutant in some of the syndromes, although the pathophysiology is still not entirely clear. The inheritance patterns include X-linked recessive, autosomal dominant, autosomal recessive, and even mitochondrial. The FA gene products appear to cooperate, and are important in the pathways involved in response to DNA damage. However, the role of this pathway in developmental defects, hematopoietic failure, and the specific malignancies in FA is not fully elucidated. The DC gene products are important for maintenance of telomere length, which may have relevance to development of aplastic anemia and malignancies, but the relation to the physical phenotype is less apparent. The role of mutations in *c-mpl* in Amega is more straightforward, since the gene codes for the receptor for thrombopoietin, which is the hormone required for megakaryocyte and platelet development; patients with mutant *c-mpl* do not have birth defects. The role of mutations in RPS19 in erythropoiesis or developmental defects in DBA patients is not obvious, and the increased frequency of osteogenic sarcomas suggests that at least that subset of patients may have a mutant tumor suppressor gene (such as p53, the mutant gene in Li-Fraumeni syndrome) [68]. Although patients with

SCN have mutations in neutrophil elastase, patients with similar mutations may have relatively benign cyclic neutropenia, or may even have normal neutrophil levels [69] [70] . The mitochondrial gene deletions in Pearson's Syndrome result in variable degrees of acidosis, and varied organ involvement due to heteroplasmy. Thus, the disorders included under the rubric "inherited **bone** marrow failure syndromes" have clinical, hematologic, oncologic, and genetic diversity.

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